Alcohol Binge Drinking: Negative and Positive Valence System Abnormalitier

Serenella Tolomeo, Jennifer A. McFarlane, Alex Baldacchino, George F. Koob, J. Douglas Steele

Department of Psychology (ST), National University of Singapore, Singapore;
Department of Medical Physics (JM), NHS Tayside, UK; Division of Population and Behavioral Science (AB), Medical School, University of St Andrews, UK;
National Institute on Alcohol Abuse and Alcoholism (GK), USA;
Division of Imaging Science and Technology (JDS), Medical School, University of Dundee, UK.

Short Title: Binge drinking and RDoC

***Keywords*:** allostasis, binge drinking, RDoC, reinforcement learning, striatum, amygdala-hippocampal complex

Abstract 181 (<250)
Main text 3,998 (<4,000)
Figures 4
Tables 0
Supplementary Materials 1

Correspondence to:
Prof Douglas Steele
M.D., PhD, MRCPsych
Medical School, University of Dundee,
Ninewells Hospital and Medical School
Dundee, UK, DD1 9SY
dsteele@dundee.ac.uk

ABSTRACT

BACKGROUND: Three million deaths occur each year due to alcohol misuse. Translational studies are crucial to translate preclinical findings to patients. Preclinical studies have highlighted abnormalities in specific brain systems with these forming the basis of allostasis theory. However, few studies have tested predictions in humans using neuroimaging.

METHODS: Here we used a Research Domain Criteria (RDoC) approach to test allostasis theory predictions of blunted positive valence system (PVS) and abnormally increased negative valence system (NVS) responses in fifty-seven binge alcohol drinking subjects and healthy controls who completed an instrumental task during fMRI.

RESULTS: As hypothesised, binge alcohol drinkers showed abnormally increased activity in NVS-linked regions such as the hippocampus and dorsal cingulate, and abnormally blunted activity in PVS-linked regions such as the striatum, compared to controls. Higher measures of problematic alcohol use were associated with more abnormal brain activity, only for binge drinkers who had been most recently drinking.

CONCLUSIONS: These results support allostasis theory predictions of abnormally increased NVS and blunted PVS responses in binge alcohol drinkers. Further similar translational neuroimaging studies are indicated, particularly focusing on the NVS.

Alcohol misuse, defined by the UK National Institute of Clinical Excellence (NICE) as harmful use of alcohol which includes binge drinking or alcohol dependency (1), is a leading cause of long-term disability worldwide (2) with three million deaths every year (3). Alcohol intoxication is characterized by euphoria and reduced anxiety, but as alcohol dependency develops over months or years, hypohedonia and decreased resilience to stress are characteristic features (4-6). Alcohol is the most commonly used intoxicating substance during adolescence and by the age of 20 years, almost a quarter of young adults report regular heavy episodic 'binge' drinking (7). For individuals who habitually binge drink, there is a 13 to 19-fold increased risk of developing alcohol dependency (8).

Considerable evidence from preclinical (6,9,10) and Positron Emission Tomography (PET) (11) studies indicates a shift from positive reinforcement to negative reinforcement as problematic alcohol use worsens. Recently, Siciliano and colleagues reported a circuit within the medial prefrontal cortex and Peri-Aqueductal Grey (PAG) as a biomarker to classify an animal's alcohol drinking phenotype (12). A better understanding of illness mechanisms will facilitate the development of better treatments; however, these remain unclear for humans. The Research Domain Criteria (RDoC) were designed to link subjective symptoms to brain function with a focus on brain circuits (13), so can facilitate forward and reverse translation between invasive preclinical studies on animals and non-invasive clinical studies. An RDoC framework modified for alcohol misuse has been recently proposed which emphasized negative emotionally, incentive salience and executive dysfunction (14).

Inconsistencies of findings reported in the literature on alcohol misuse were highlighted in a recent meta-analysis (15), attributed to conflation of brain responses

to reward anticipation vs. reward outcome events, use of drug vs. non-drug stimuli and different brain abnormalities at different stages of alcohol misuse (e.g. harmful alcohol use, dependence, abstinence). Whilst many studies have investigated reward-linked abnormalities, far fewer neuroimaging studies have tested for abnormalities in the human stress/aversive (RDoC Negative Valence) system, and for abnormalities in negative reinforcement ('dark side of addiction'), which pre-clinical work has emphasized is crucial for the development and maintenance of alcohol dependence (4,5,10).

Progressive stages of alcohol misuse, from occasional to frequent binge drinking, to alcohol dependence, can be characterized as progressive 'allostatic' changes, consisting of adaptation of the brain to repeated alcohol exposure (Figure 1). Such neuroadaptations comprise down-regulation of the reward system (in allostasis theory terms a 'within-system' abnormality) and up-regulation of the stress-negative emotional system (allostasis 'between-system' abnormality) (6,10). In RDoC terms, the former is progressive blunting of the Positive Valence System (PVS) and the latter sensitization of the Negative Valence System (NVS). Negative reinforcement, driven by negative emotional states with transient relief achieved by compulsive intoxication, is hypothesized to drive alcohol dependence, rather than impulsive consumption which characterizes early-stage alcohol misuse (4,5,16).

Abnormalities in various neurotransmitters including dopamine, gamma-amino-butyric acid (GABA) and glutamate, have been reported in pre-clinical studies (10) and also can be inferred from clinical observations: e.g. presence of hypohedonia, abnormal salience of alcohol (craving), use of a benzodiazepine reducing regimen for newly abstinent dependent patients to avoid seizures (1). The dopaminergic system

can be non-invasively studied in humans using event-related fMRI (17-20). Preclinical studies report that GABA and glutamate act directly on ligand-gated receptor channels in the central-basolateral amygdala and brain stem, regions implicated in alcohol-related positive and negative reinforcement (21). GABA and glutamate can be non-invasively studied in humans using Magnetic Resonance Spectroscopy (MRS) (22) and GABA and glutamate are implicated as modulating neural encoding of reward value (23-25). Here we used a combined reward-gain and loss-avoidance instrumental task during fMRI (18,26) and MRS to study GABA and glutamate, to test for hypothesised abnormalities in habitual binge drinking non-dependent adults using an RDoC approach. As with previous work on depressive illness, *unsuccessful* loss avoidance (experience of a loss) was assumed to be linked to NVS activation, as loss events are experienced as aversive in contrast to *successful* loss-avoidance which has similarities to a reward (26,27) (PVS) and loss is an aversive event linked to depression symptoms (28).

We chose to study binge drinkers rather than alcohol-dependent subjects as the former have a very high (13 to 19-fold) risk of developing alcohol dependence (8), so observed functional brain abnormalities may be risk factors for developing dependency. Additionally, alcohol is neurotoxic and alcohol dependency is commonly associated with brain structure abnormalities, complicating interpretation of functional brain imaging results. Allostasis is a continuous process so we expected binge drinkers to be towards the left of Figure 1(B) and dependent drinkers towards the right.

Allostasis theory (Figure 1) (6,10,29) was used to construct translational hypotheses for binge drinkers compared to controls testable using fMRI: i) *increased*

activation of NVS-linked regions (e.g. anterior mid-cingulate cortex, bilateral anterior insula, medial hypothalamus, periaqueductal grey, amygdala-hippocampal complex) to aversive events (26,30); ii) *blunted* reward-gain (win) activity and decreased reward value encoding in PVS–linked brain regions (e.g. striatum, rostral anterior cingulate, amygdala-hippocampal complex) (26). We compared weekend-only habitual binge drinkers, by which we mean subjects with a stable pattern of weekend-only binge drinking, to healthy controls, with binge drinkers randomly assigned to scanning on either Friday or Monday. This was because we aimed to capture the 'b process' period (Figure 1) in those scanned on a Monday and the pre-'a process' period for those scanned on a Friday. Consequently we hypothesised that: iii) transient binge drinking fMRI –measured abnormalities would be most marked in binge drinkers who had been most recently drinking; i.e. the group scanned on a Monday. Finally we hypothesised (Figure 1) that iv) MRS-measured abnormalities would comprise *downregulation* of GABA and/or upregulation of glutamate.

METHODS AND MATERIALS

Participants

The study was approved by the East of Scotland Research Ethics Service (14/ES/0061) with each participant providing written informed consent. A binge drinking group comprised twenty males and eighteen females all of whom described binge drinking only at the weekend. No binge drinkers met criteria for current or past alcohol dependency. Half of this group was scanned before the weekend on a Friday, the others after the weekend on a Monday. The assignment was done alternately to Friday or Monday scanning as recruitment progressed. Before scanning we checked with subjects that there had been no drinking during the week.

A group of nineteen healthy controls (thirteen males, six females) were also scanned. Nineteen healthy controls were assessed for a history of past binge drinking or dependence and any current or past psychiatric and neurological disease. None of the subjects satisfied the criteria for alcohol or other drug dependence and none were taking medications. All volunteers had normal or corrected-to-normal vision and none had a history of neurological problems. Data from one control subject was excluded due to movement during scanning. Data from the remaining fifty-six participants were used in all subsequent analyses.

Diagnoses were made according to the MINI-Plus (v5) semi-structured interview and the Alcohol Use Disorders Identification Test (AUDIT) was used to help quantify drinking patterns, with binge drinking identified according to the National Institute on Alcohol Abuse and Alcoholism (NIAAA) definition: consumption of alcohol to a blood alcohol level of 0.08 g/dL, which typically occurs after 4 drinks for women and

5 drinks for men when consumed in 2 hours. The Severity of Alcohol Dependence Questionnaire (SADQ) was also used to quantify drinking patterns: although no subjects were alcohol dependent, the scale can be interpreted as providing a continuous measure of alcohol misuse severity, similar to the AUDIT. Mood symptoms were quantified using the 17-item Hamilton (HAM) Depression Rating Scale and Beck Depression Inventory-II scales. Anxiety symptoms were measured using the Spielberger state (STAI-S) and trait (STAI-T) rating scales. IQ was estimated using the National Adult Reading Test (NART). For details on the above see Supplementary Information. None of the subjects used non-alcohol drugs with the exception of cigarettes which was balanced across groups. Clinical details and demographics are provided in Supplimentary Materials, Table S1.

Behavioral Paradigm

Figure 2 shows the reward-gain and loss-avoidance instrumental learning task used during fMRI, which we also have previously used in studies of opioid dependent subjects without a history of binge alcohol drinking or depression (18), and patients with treatment-resistant major depressive disorder (MDD) without a history of alcohol or drug misuse (26).

The RDoC Matrix includes 'loss' as a NVS construct and 'reward learning' as a PVS construct (31). Notably then, brain responses to loss were the NVS fMRI measures; brain responses to reward were the PVS fMRI measures. The task has three possible outcomes: rewarding ('win'), aversive ('lose') and neither win nor lose ('nothing'). Volunteers were told that the aim of the task was to maximize winning and to avoid losing points ('vouchers') as much as possible, and they had to learn to

do this by trial and error. 'Win trials' had two possible outcomes: 'You Win' or 'Nothing'. 'Lose trials' had two possible outcomes: 'You Lost' or 'Nothing'. One pair of novel fractal images was therefore associated with each type of outcome and the association between a given pair of fractal images and either win or loss was randomized across participants. The probability of win/loss fractal pairs had a fixed high probability (70%) and a fixed low probability (30%). Each session had 60 trials with each session lasting 13 min in total and 3 sessions per subject. The reward-gain and loss-avoidance trials were presented in a pseudo-random order.

Image Acquisition, Pre-processing and Analyses

For each participant, functional whole-brain images were acquired using a 3T Siemens Tim Trio scanner. A total of 37 slices were obtained per volume, with an echo-planar imaging sequence comprising a repetition time (TR) 2.5 sec, echo time (TE) 30 ms, flip angle 90 degrees, field of view 22.4 cm, matrix 64x64, with a voxel size of 3.5x3.5x3.5 mm.

Images were visually inspected for artefacts and pre-processed using Statistical Parametric Mapping (SPM) (http://www.fil.ion.ucl.ac.uk/spm/). First, images were realigned and co-registered to the SPM Montreal Neurological Institute (MNI) anatomical space echo-planar template. The average realigned co-registered image for each subject was then used to spatially normalize each realigned co-registered volume and smoothed with an 8 mm full width half maximum kernel. For a random-effects analysis, data from each subject were analyzed separately (first-level analyses) before summary statistical 'beta' images were tested at the group level (second level analyses). For testing NVS and PVS hypotheses, a first-level analysis was done

comparing event-related activity at the outcome time for 'loss' vs 'nothing' and 'win' vs 'nothing' binary feedback events.

For second-level random-effects analyses, summary statistical images from the first-level analyses for each subject were separately entered into second-level analyses to test for within-group activations/deactivations (one group t-test) and between-group differences (binge drinkers vs. controls; two group t-test). Correlations with binge alcohol use severity (AUDIT and SADQ scales) and mood, anhedonia and anxiety symptoms (BDI, STAI) were also calculated for the binge drinking group alone, to test whether symptom severity correlations were consistent with between-group differences. The reason for the correlation analyses was that between-groups differences may be influenced by unrecognized factors so we sought convergent evidence using binge drinking-related continuous measures. In addition, correlations with spectroscopy measures (see below) were calculated to test whether variation in these ratios was associated with fMRI activations/deactivations.

Significance was defined as $p<0.01$ at a whole-brain, Family-Wise Error corrected level, comprising a simultaneous requirement for a voxel threshold ($p<0.05$) and a minimum cluster extent (120 voxels) identified using a commonly used Monte-Carlo method (32). All figures were thresholded at this significance level. There was a difference in average age between controls and binge drinkers so correlations between age and the signals of interest were tested for. There were no significant correlations for brain regions of interest which meant age need not be used as a covariate in the second-level analyses. However, when this was done as a check, as expected it did not have a significant effect on the results. Region of interest (ROI)

analyses used the principal eigenvariate as the summary measure of brain response in a 10 mm diameter sphere (33).

MR Spectroscopy and Analyses

Mescher-Garwood Point Resolved Spectroscopy (MEGA-PRESS) (34) was used to acquire GABA+ and combined glutamate-glutamine (GLX) signals (Figure 1). This sequence used a TR 1.5 s, TE 68 ms and region of interest (ROI) 2 x 2.5 x 4 cm^3 compromising 256 signals for each spectrum. The total spectroscopy acquisition time was 13 minutes and the standard Siemens implementation used CHESS water suppression (35). The MRS ROI was located in the anterior mid-cingulate cortex (aMCC) (Figure 2) which was chosen as it has been reported to exhibit abnormal functional activity with binge alcohol use and intoxication (36), with the region also having minimal artefactual signal dropout unlike more anatomically inferior areas such as the nucleus accumbens (NA).

Gannet software (http://www.gabamrs.com/) was used to extract for each subject the following: i) width of the fitted GABA signals calculated using a Gaussian model (GABA+FWHM) (34), ii) integral area under the curve for the GABA+ peak (GABA+ Area), iii) creatinine (Cr) to water area ratio (Cr/H_20), iii) fitting error of the spectroscopy LCM model (FtErr (Cr/H_20), iv) GABA+ concentration calculated in units relative to water ($GABA+/H_20$) and v) as an integral ratio relative to Creatine (GABA+/Cr). The same information was acquired for modelling the GLX signal: GLX concentration calculated in units relative to water and as an integral ratio relative to Creatine (GLX /Cr), width of the fitted GLX signals, integral area of GLX

peak, fit error of the LCM model. SPSS was used to test for significant differences between subjects scanned on Mondays and Friday.

RESULTS

Behavioral Analyses

Decision making behavior was well matched between binge drinking and control groups (Supplementary Information) which facilitated interpretation of fMRI results. An exploratory analyses of behavioral data from binge drinkers found alcohol Units and higher anxiety ratings (STAI-T) correlated negatively with total number of rewards achieved ($p<0.05$) and number of choices for the high reward value (70% chance win) fractal ($p<0.05$).

Negative Valence System

During loss events, the hippocampus was abnormally increased in activity (two group t-test) in binge drinkers as a whole (i.e. combining Friday and Monday scanned subjects) relative to controls (36, -30, -8) t=3.53 and (-32, 40, -6) t=3.07 (Figure 3A and B) (see also Supplementary Information Table S2). This was caused by consistent deactivation in controls and variable blunted deactivation in binge drinkers (Figure 2C; $p<0.001$). With loss events, binge drinkers (but not controls) strongly activated the anterior mid-cingulate cortex (aMCC)/dorsomedial prefrontal cortex (dmPFC) (-6,28,36) t=5.15 (Figure 3D) and brain responses in a 10 mm diameter ROI centered at the same region correlated positively with years of alcohol misuse (Figure 2E). There was a significant positive correlation with Units of alcohol and midbrain PAG activity (0, -24, -12) t=3 (Figure 3F), and Units of alcohol and PAG activity ($F_{1,18}=6.9$, $p=0.018$) (Figure 2G). However when comparing Friday with Monday binge drinkers, during loss events, there were no significant between-group differences.

In summary, brain activations to loss were abnormally increased in the hippocampus of binge drinkers compared to controls, and activation in the aMCC and PAG correlated positively with ratings of increased alcohol use in binge drinkers who had been recently drinking (Monday group).

Positive Valence System

During win events, as expected (26) heathy controls strongly activated the striatum (-10,8,-6) t=8.05; (12,8,-14) t=7.13, subgenual anterior cingulate/rostral medial prefrontal cortex (6,48,-10) t=6.39, medial temporal lobe (comprising amygdala (20,-6,-24) t=3.31; (-28,-4,-18) t=3.83 and amygdala-hippocampal complex (-30,-12,-20) t=4.11; (22,-18,-18) t=4.53) and posterior cingulate (4,-46,38) t=4.73 (Figure 4A). In comparison, during win events binge drinkers as a whole exhibited significantly blunted activation (two group t-test) in the striatum ((-16,8,10) t=4.04); (14,6,-14) t-4.0; (24,10,18) t=3.67; (-18,12,26) t=2.52) and amygdala (16,0,-18) t=3.96; (-24,0,-18) t=2.66 (Figure 3 C; $p<0.001$, see also Supplementary Information Table S3).

Consistent with the between-groups finding of blunted reward-linked activation in binge drinkers, there were significant negative correlations for binge drinkers scanned on a Monday: i) AUDIT ratings negatively correlated with reward activations in the bilateral striatum (26, 20, -12) t=4.2, (-20, 22, -8) t=3.6 and hippocampus (28, -30, -14) t=5.68; ii) *alcohol units* negatively correlated with bilateral hippocampus (-34, -26, -24) t=4.38; (28, -30, -16) t=4.8, amygdala (34, -8, -18) t=3.32 and striatal (-24, 18, 0) t= 2.9 reward activity; and iii) *years of alcohol use* negatively correlated with bilateral striatum (-24, 18, 0) t=3, (24, -14, 8) t=3.2. In contrast, no significant correlations between alcohol measures and brain activity were

found for binge drinkers scanned on a Friday were found. Comparing binge drinkers scanned on a Monday and Friday, during win events there were no significant between-group differences.

In summary, consistent with hypotheses, reward-gain brain activations were blunted in the bilateral striatum in binge drinkers compared to healthy controls. Negative correlations between alcohol use ratings and blunted reward activation were present just after binge drinking (Monday group), although there were no significant differences between binge alcohol drinking groups.

MR Spectroscopy and Analyses

As hypothesised, the GLX/Cr and GABA/GLX ratio differed (p=0.04 and p=0.05 respectively) between binge alcohol drinking groups, with the binge drinkers scanned on Monday having higher and lower ratios respectively (Supplementary Information, Table S1). A positive correlation was found between the glutamate + glutamine (GLX)/creatine (Cr) ratio and the number of high value reward choices (r=0.39, p=0.02). For loss events (NVS), using an ROI centered at our previously reported midbrain location (0, -20, -2) (26), we found a significant ($F_{1,15}$=10.5, p=0.006) negative correlation with GABA/Cr (Figure 3H).

DISCUSSION

Here we tested hypotheses of abnormally increased NVS brain activity and blunted PVS activity in binge alcohol drinkers based on preclinical and human PET studies (4,5,9) using an RDoC approach. NVS-linked brain regions and systems include Gray's hierarchical defense system (e.g. cingulate, amygdala-hippocampal system, medial thalamus and PAG) (30), with these linked to alcohol withdrawal (e.g. extended amygdala) and alcohol craving (e.g. hippocampus, anterior cingulate) (4,5,29). PVS-linked brain regions and systems mediating positive reinforcement are well established (e.g. striatum, dopamine and opioid system) (4,5).

As hypothesised, binge drinkers had abnormally increased brain responses to loss events (NVS) in the amygdala and hippocampus. Specifically, healthy controls deactivated the hippocampus in response to loss events in contrast to binge drinkers, with hippocampal overactivity in binge drinkers due to a failure to deactivate the hippocampus. Using the same paradigm in non-binge drinking patients with treatment-resistant MDD, we also reported a failure to deactivate the hippocampus on loss events (26), interpreting overactivity in MDD as consistent with Deakin & Graeff's suggestion (37) as reflecting excessive encoding of aversive information (26) and in humans depressive ruminations (37). In the context of alcohol misuse, the hippocampus has been linked to alcohol preoccupation and craving, with the extended amygdala (central nucleus of amygdala, bed nucleus of stria terminalis, NA shell) being important for adverse effects on reward function produced by stress that drives alcohol use (29). There is compelling pre-clinical evidence for increased activity in brain stress systems mediated by neurochemical changes in the extended amygdala, such as Corticotrophin-Releasing Factor, dynorphin and norepinephrine

(29) with these neuromodulators acting on brain structures identified as part of the hierarchical defense system.

Consistently increased dorsal medial cortex activity with loss events in binge drinkers was also found, the magnitude of which correlated with years of alcohol use. The aMCC/dmPFC is strongly implicated in negative affect, cognitive control and pain (38) and is part of the NVS. Lesions in the aMCC (anterior cingulotomy; ACING) have been used to treat treatment-resistant MDD without alcohol or substance misuse (39) and we have argued the aMCC has a causal role in negative affect and cognitive control (40). In the context of alcohol misuse, the anterior cingulate has been linked with alcohol preoccupation and craving (4). ACING has been used for the treatment of alcohol dependence (41) and aMCC deep brain stimulation has been reported to suppress alcohol craving (42).

Here we found PAG activity during loss events correlated positively with the number of Units of alcohol and negatively with GABA/Cr only in the binge drinking group scanned on Monday after recent drinking. Preclinical work has strongly linked the PAG to aversive experiences such as panic (37) and 10-40% of patients with alcohol misuse have a panic-related anxiety disorder (43). Preclinical studies have reported serotonin inhibits panic behavior (37), plasma serotonin and central transporters were reduced during alcohol withdrawal (44,45) and alcohol withdrawal-induced hyperalgesia is partially mediated by amygdala projections to the PAG (46). Notably, we reported PAG activation during loss events using the same behavioral paradigm in MDD patients without alcohol misuse (26). A recent review highlighted the PAG's role in the NVS in psychiatric disorders and argues the PAG may have a pivotal role in the 'dark side' of addiction (47). Our findings suggests that whilst

differences between binge drinkers scanned on Monday compared to Friday are likely state dependent and reversible, the differences between binge drinkers as a whole and controls may not and instead reflect binge drinking, or a pre-existing vulnerability factor for developing binge drinking. Longitudinal neuroimaging studies could help disentangle factors underlying pre-existing brain vulnerability factors, developmental factors, alcohol misuse allostasis brain changes and gender differences (48).

As hypothesised, binge drinkers showed blunted striatal reward activity (RDoC PVS, allostasis within-system abnormality) relative to controls. Using the same behavioral paradigm and scanning parameters, we reported a similar abnormality in treatment-resistant major depressive disorder (MDD) without alcohol misuse (26) which has been replicated in our independent studies and by many other groups (19,49-51). Previously we reported evidence for increased NVS responses and blunted PVS responses in treatment-resistant MDD without alcohol misuse (52). Here we report a similar pattern in binge alcohol users without MDD. Early adversity is a risk factor for later life psychiatric disorders such as alcohol misuse and MDD (53) associated with enduring stress sensitization (54). Increased NVS responses, as a consequence of early adversity interacting with genetic vulnerability (55), may be a common risk factor predisposing to both alcohol misuse and MDD, with allostasis theory suggesting repeated excessive exposure to alcohol worsens this predisposition.

Notably, these changes in PVS and NVS-linked brain regions are consistent with the hypothesis of allostatic changes in humans caused by repeated excessive use of alcohol (10) increasing the risk of dependency. Repeated engagement of opponent processes, without time for the brain's emotional systems to re-establish homeostasis, generates negative emotional states (6) which have similarities to symptoms of MDD.

Importantly we used reward stimuli unrelated to alcohol consumption, as with our previous study on opioid dependency (18). This was because drug-related cues (e.g. pictures of alcohol or other drug containers) have been associated with increased activity in brain regions such as the striatum (56) and we have argued it is important to discriminate non-drug and drug-related stimuli (18). In addition, our task (18,26) used different neutral comparison conditions for active 'win' or 'lose' feedback, as other contrasts (e.g. directly comparing reward vs. loss brain responses) can give different results (15).

The strengths of the present study are use of an RDoC approach to test for functional brain abnormalities in binge drinkers without marked brain structure abnormalities which are common in alcohol dependent patients. There are however limitations as avenues for future work. Allostasis theory provides a rich source of hypotheses for non-invasive neuroimaging studies on humans. Consequently, we did not aim to test all possible hypotheses and focused on fMRI measures which we have experience of obtaining in other clinical groups (18,26,49). We did not include a correction for multiple ROI comparisons. Additionally, larger independent studies including alcohol dependent patients would be informative.

In summary, consistent with predictions from preclinical and radioisotope imaging studies, we found evidence for abnormal allostatic brain responses in binge alcohol drinkers: in RDoC terms increased NVS and blunted PVS response abnormalities. The use of a translational RDoC approach in humans is a new innovative approach to the study of the neurobiology of addiction. Further investigation of alcohol misuse in patients is indicated, particularly allostasis theory between system-abnormalities and

the RDoC negative valence system, which allostasis theory emphasizes as important for development and maintenance of the more severe types of alcohol misuse.

ACKNOWLEDGEMENTS AND DISCLOSURES

This work was supported by an award from Dundee University Medical School (ref. AT27) to ST and JDS. Spectroscopy was supported by an unrestricted 'Work in Progress' agreement with Siemens. The funding sources played no part in the design of the study, analyses and interpretation of the data, nor manuscript preparation. The authors have no competing financial interests or conflicts of interest. We are grateful to Dr Victoria Gradin who implemented the first version of the behavioral task in Presentation, Dr Blair Johnston who translated the task to Matlab and Mairi Stirling and Sarah Gray for help with recruitment.

ARTICLE INFORMATION

From the Department of Psychology (ST), National University of Singapore, Singapore; Department of Medical Physics (JM), NHS Tayside, UK; Division of Population and Behavioral Science (AB), Medical School, University of St Andrews, UK; National Institute on Alcohol Abuse and Alcoholism (GK), USA; Division of Imaging Science and Technology (JDS), Medical School, University of Dundee, UK Address correspondence to Prof Douglas Steele, M.D., PhD, MRCPsych, Medical School, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK, DD1 9SY, dsteele@dundee.ac.uk

REFERENCES

1 NICE. Alcohol-use disorders: diagnosis, assessment and management of harmful drinking and alcohol dependence (CG115). NICELondon; 2011.

2 Degenhardt L, Charlson F, Ferrari A, Santomauro D, Erskine H, Mantilla-Herrara A, et al. (2018): The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Psychiatry. 5:987-1012.

3 WHO. Alcohol - https://www.who.int/news-room/fact-sheets/detail/alcohol. 2018. https://www.who.int/news-room/fact-sheets/detail/alcohol. Accessed 4/1/2020 2018.

4 Koob GF, Volkow ND. (2010): Neurocircuitry of addiction. Neuropsychopharmacology. 35:217-38.

5 Koob GF, Volkow ND. (2016): Neurobiology of addiction: a neurocircuitry analysis. The lancet Psychiatry. 3:760-73.

6 Koob GF, Le Moal M. (2001): Drug addiction, dysregulation of reward, and allostasis. Neuropsychopharmacology. 24:97-129.

7 Windle M. (2016): Drinking Over the Lifespan: Focus on Early Adolescents and Youth. Alcohol research : current reviews. 38:95-101.

8 Waszkiewicz N, Galinska-Skok B, Nestsiarovich A, Kulak-Bejda A, Wilczynska K, Simonienko K, et al. (2018): Neurobiological Effects of Binge Drinking Help in Its Detection and Differential Diagnosis from Alcohol Dependence. Disease markers. 2018:1-9.

9 Ahmed SH, Koob GF. (1998): Transition from moderate to excessive drug intake: change in hedonic set point. Science. 282:298-300.

10 Koob GF, Schulkin J. (2019): Addiction and stress: An allostatic view. Neurosci Biobehav Rev. 106:245-62.

11 Volkow ND, Fowler JS, Wang GJ, Baler R, Telang F. (2009): Imaging dopamine's role in drug abuse and addiction. Neuropharmacology. 56 Suppl 1:3-8.

12 Siciliano CA, Noamany H, Chang CJ, Brown AR, Chen X, Leible D, et al. (2019): A cortical-brainstem circuit predicts and governs compulsive alcohol drinking. Science. 366:1008-12.

13 Sanislow CA, Quinn KJ, Sypher I. in *Encyclopedia of Clinical Psychology* (eds Cautin RL, Lilienfeld SO) (John Wiley & Sons, 2015).

14 Kwako LE, Schwandt ML, Ramchandani VA, Diazgranados N, Koob GF, Volkow ND, et al. (2019): Neurofunctional Domains Derived From Deep Behavioral Phenotyping in Alcohol Use Disorder. Am J Psychiatry. 176:744-53.

15 Luijten M, Schellekens AF, Kuhn S, Machielse MW, Sescousse G. (2017): Disruption of Reward Processing in Addiction : An Image-Based Meta-analysis of Functional Magnetic Resonance Imaging Studies. JAMA psychiatry. 74:387-98.

16 Koob GF. (2013): Negative reinforcement in drug addiction: the darkness within. Curr Opin Neurobiol. 23:559-63.

17 Pessiglione M, Seymour B, Flandin G, Dolan RJ, Frith CD. (2006): Dopamine-dependent prediction errors underpin reward-seeking behaviour in humans. Nature. 442:1042-5.

18 Gradin VB, Baldacchino A, Balfour D, Matthews K, Steele JD. (2014): Abnormal brain activity during a reward and loss task in opiate-dependent patients receiving methadone maintenance therapy. Neuropsychopharmacology. 39:885-94.

19 Gradin VB, Kumar P, Waiter G, Ahearn T, Stickle C, Milders M, et al. (2011): Expected value and prediction error abnormalities in depression and schizophrenia. Brain. 134:1751-64.

20 Gu X, Lohrenz T, Salas R, Baldwin PR, Soltani A, Kirk U, et al. (2015): Belief about nicotine selectively modulates value and reward prediction error signals in smokers. Proc Natl Acad Sci U S A. 112:2539-44.

21 Koob GF, Buck CL, Cohen A, Edwards S, Park PE, Schlosburg JE, et al. (2014): Addiction as a stress surfeit disorder. Neuropharmacology. 76 Pt B:370-82.

22 Puts NA, Edden RA. (2012): In vivo magnetic resonance spectroscopy of GABA: a methodological review. Progress in nuclear magnetic resonance spectroscopy. 60:29-41.

23 Jocham G, Hunt LT, Near J, Behrens TE. (2012): A mechanism for value-guided choice based on the excitation-inhibition balance in prefrontal cortex. Nat Neurosci. 15:960-1.

24 Hare TA, Schultz W, Camerer CF, O'Doherty JP, Rangel A. (2011): Transformation of stimulus value signals into motor commands during simple choice. Proc Natl Acad Sci U S A. 108:18120-5.

25 Gershman SJ, Pesaran B, Daw ND. (2009): Human reinforcement learning subdivides structured action spaces by learning effector-specific values. J Neurosci. 29:13524-31.

26 Johnston BA, Tolomeo S, Gradin V, Christmas D, Matthews K, Steele JD. (2015): Failure of hippocampal deactivation during loss events in treatment-resistant depression. Brain. 138:2766-76.

27 Rolls ET. The Brain and Emotion. Oxford University PressOxford; 1999.

28 Beck AT. Cognitive Theory of Depression. J. Wiley and SonsNew York; 1979.

29 Koob GF, Le Moal M. (2008): Addiction and the brain antireward system. Annu Rev Psychol. 59:29-53.

30 Gray JA, McNaughton N. The Neuropsychology of Anxiety: An Enquiry into the Functions of the Septo-Hippocampal System. Oxford University PressOxford; 2000.

31 NIMH. RDoC Matrix. 2020. https://www.nimh.nih.gov/research/research-funded-by-nimh/rdoc/constructs/rdoc-matrix.shtml. Accessed 14/6/20.

32 Slotnick SD, Moo LR, Segal JB, Hart J, Jr. (2003): Distinct prefrontal cortex activity associated with item memory and source memory for visual shapes. Brain research Cognitive brain research. 17:75-82.

33 Poldrack RA. (2007): Region of interest analysis for fMRI. Social cognitive and affective neuroscience. 2:67-70.

34 Mullins PG, McGonigle DJ, O'Gorman RL, Puts NA, Vidyasagar R, Evans CJ, et al. (2014): Current practice in the use of MEGA-PRESS spectroscopy for the detection of GABA. Neuroimage. 86:43-52.

35 Ogg RJ, Kingsley PB, Taylor JS. (1994): WET, a T1- and B1-insensitive water-suppression method for in vivo localized 1H NMR spectroscopy. J Magn Reson B. 104:1-10.

36 Goldstein RZ, Volkow ND. (2011): Dysfunction of the prefrontal cortex in addiction: neuroimaging findings and clinical implications. Nat Rev Neurosci. 12:652-69.

37 Deakin J. (2013): The origins of '5-HT and mechanisms of defence' by Deakin and Graeff: a personal perspective. J Psychopharmacol. 27:1084-9.

38 Shackman AJ, Salomons TV, Slagter HA, Fox AS, Winter JJ, Davidson RJ. (2011): The integration of negative affect, pain and cognitive control in the cingulate cortex. Nature Reviews Neuroscience. 12:154-67.

39 Steele JD, Christmas D, Eljamel MS, Matthews K. (2008): Anterior cingulotomy for major depression: clinical outcome and relationship to lesion characteristics. Biol Psychiatry. 63:670-7.

40 Tolomeo S, Christmas D, Jentzsch I, Johnston BA, Sprenglemeyer R, Matthews K, et al. (2016): A causal role for the anterior mid-cingulate cortex in negative affect and cognitive control. Brain. 139:1844-54.

41 Ma S, Zhang C, Yuan TF, Steele JD, Voon V, Sun B. (2019): Neurosurgical treatment for addiction: Lessons from an untold story in China and a path forward. National Science Review. (in press).

42 De Ridder D, Manning P, Glue P, Cape G, Langguth B, Vanneste S. (2016): Anterior Cingulate Implant for Alcohol Dependence: Case Report. Neurosurgery. 78:E883-93.

43 Cox BJ, Norton GR, Swinson RP, Endler NS. (1990): Substance abuse and panic-related anxiety: a critical review. Behaviour research and therapy. 28:385-93.

44 Patkar AA, Gopalakrishnan R, Naik PC, Murray HW, Vergare MJ, Marsden CA. (2003): Changes in plasma noradrenaline and serotonin levels and craving during alcohol withdrawal. Alcohol and Alcoholism. 38:224-31.

45 Heinz A, Ragan P, Jones DW, Hommer D, Williams W, Knable MB, et al. (1998): Reduced central serotonin transporters in alcoholism. Am J Psychiatry. 155:1544-9.

46 Avegno EM, Lobell TD, Itoga CA, Baynes BB, Whitaker AM, Weera MM, et al. (2018): Central Amygdala Circuits Mediate Hyperalgesia in Alcohol-Dependent Rats. J Neurosci. 38:7761-73.

47 George DT, Ameli R, Koob GF. (2019): Periaqueductal Gray Sheds Light on Dark Areas of Psychopathology. Trends Neurosci. 42:349-60.

48 Sawyer KS, Oscar-Berman M, Barthelemy OJ, Papadimitriou GM, Harris GJ, Makris N. (2017): Gender dimorphism of brain reward system volumes in alcoholism. Psychiatry research Neuroimaging. 263:15-25.

49 Steele JD, Kumar P, Ebmeier KP. (2007): Blunted response to feedback information in depressive illness. Brain. 130:2367-74.

50 Kumar P, Waiter G, Ahearn T, Milders M, Reid I, Steele JD. (2008): Abnormal temporal difference reward-learning signals in major depression. Brain. 131:2084-93.

51 Rupprechter S, Romaniuk L, Series P, Hirose T, Hawkins E, Sandu-Giuraniuc A-L, et al. (2020): Blunted Medial Prefrontal Cortico-Limbic Reward-Related Effective Connectivity and Depression. Brain.

52 Johnston BA, Steele JD, Tolomeo S, Christmas D, Matthews K. (2015): Structural MRI-Based Predictions in Patients with Treatment-Refractory Depression (TRD). PLoS One. 10:e0132958.

53 Gershon A, Sudheimer K, Tirouvanziam R, Williams LM, O'Hara R. (2013): The long-term impact of early adversity on late-life psychiatric disorders. Current psychiatry reports. 15:352.

54 Bunea IM, Szentagotai-Tatar A, Miu AC. (2017): Early-life adversity and cortisol response to social stress: a meta-analysis. Translational psychiatry. 7:1274.

55 Binder EB. (2017): Understanding gene x early adversity interactions: possibilities for insight in the biology of psychiatric disorders. European archives of psychiatry and clinical neuroscience. 267:183-85.

56 Tanabe J, Reynolds J, Krmpotich T, Claus E, Thompson LL, Du YP, et al. (2013): Reduced neural tracking of prediction error in substance-dependent individuals. Am J Psychiatry. 170:1356-63.

57 Solomon RL, Corbit JD. (1974): An opponent-process theory of motivation. I. Temporal dynamics of affect. Psychol Rev. 81:119-45.

58 Solomon RL. (1980): The Opponent-Process Theory of Acquired Motivation - the Costs of Pleasure and the Benefits of Pain. American Psychologist. 35:691-712.

59 Koob GF. (2003): Alcoholism: allostasis and beyond. Alcoholism, clinical and experimental research. 27:232-43.

60 Karadayian AG, Busso MJ, Feleder C, Cutrera RA. (2013): Alterations in affective behavior during the time course of alcohol hangover. Behav Brain Res. 253:128-38.

61 Koob GF. (2013): Addiction is a Reward Deficit and Stress Surfeit Disorder. Frontiers in psychiatry. 4:72.

62 Koob GF, Arends MA, McCracken M, Le Moal M. What is Addiction? Neurobiology of Addiction. Volume 1, Chapter 1, New York: Academic Press; 2019.

Figure 1. Allostasis theory

Single first episode alcohol exposure (A) with positive (+) mood ('a process') during drinking followed by a post-intoxication 'hangover' comprising negative (-) mood ('b process') (6,57-59). With repeated episodes of intoxication, the 'a process' diminishes and the depth of the 'b process' increases with low mood and anxiety (60) and an increase in duration (6,57,58,61). Note that the the negative affect state is hypothesized to begin following the first intoxication binge as reflected in an opponent process, dysphoric-like response, both in humans and animals (62) (B) Frequent repeated alcohol use, such that the 'b process' does not have time to fully return to homeostasis, results in mood drifting downwards and 'hyperkatifeia' defined as a negative valenced longer duration mood state with stress vulnerability (6,59,61). Abbreviations: gamma-aminobutrric acid (GABA), dopamine (DA), conticotrophin releasing factor (CRF), neuropeptide Y (NPY). Figure adapted from multiple sources.

Figure 2. Behavioral paradigm

The (A) reward–gain and (B) loss-avoidance instrumental learning task. (C) Anterior mid-cingulate cortex region selected for (D) GABA and (E) GLX measurement. Gamma-Amino-Butyric Acid = GABA; Glutamate-glutamine = GLX.

Figure 3. Negative Valence System

Brain responses to feedback of unsuccessful loss-avoidance: (A) deactivation of the hippocampus in the control group and (B) significantly less hippocampal deactivation in the binge drinkers compared to controls and (C) with a region of interest analysis

(two-group t-test $p<0.001$), (D) activation of the anterior mid-cingulate cortex in binge drinkers which (E) correlated with years of alcohol use ($p<0.018$). A posterior brainstem region including the periaqueductal grey (PAG) activated in binge drinkers during unsuccessful loss avoidance (F) which correlated positively with of alcohol units ($p=0.018$) (G) and negatively ($p=0.006$) with GABA/Cr for binge drinkers scanned on a Monday (H). All brain regions significant at $p<0.01$ whole brain corrected.

Figure 4. Positive Valence System

Brain responses to feedback of reward events (A) activation of bilateral striatum in the control group and (B) significantly less striatum activation in the binge drinkers compared to controls (C) with a region of interest analysis (two-group t-test $p<0.001$). All brain regions significant at $p<0.01$ whole brain corrected.

Figure 1

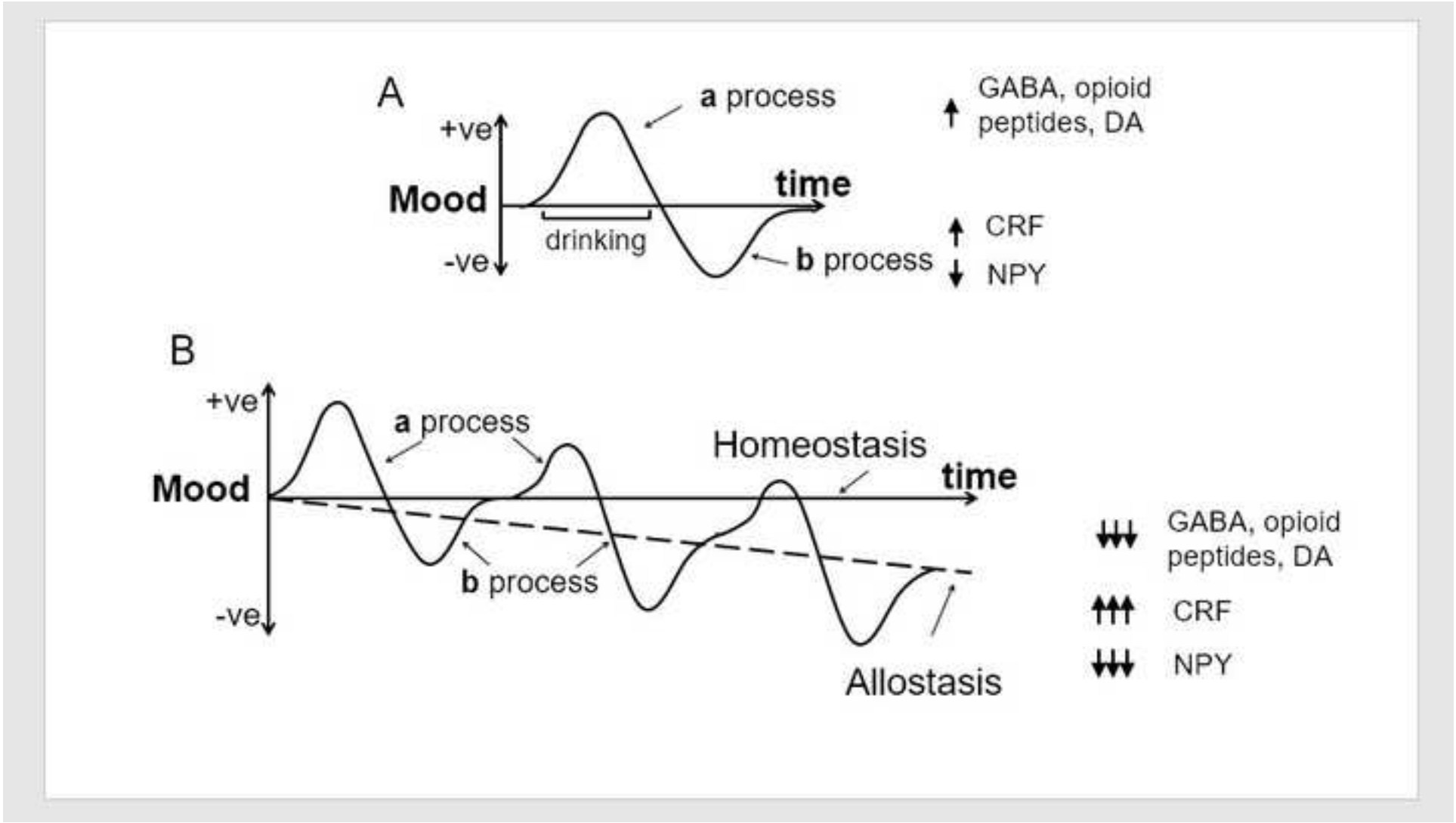


Figure 2

Click here to access/download;Figure;fig1.jpg

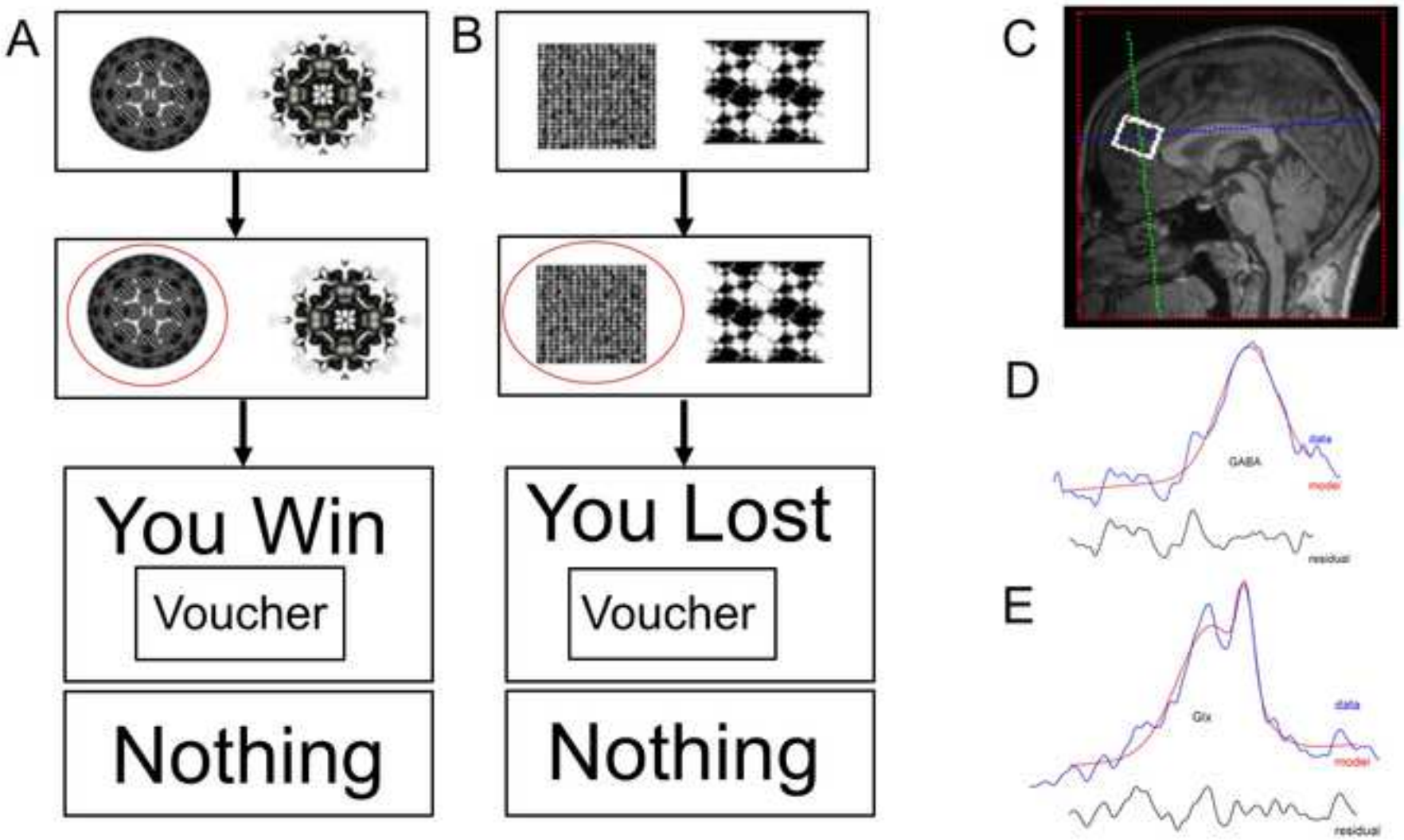


Figure 3

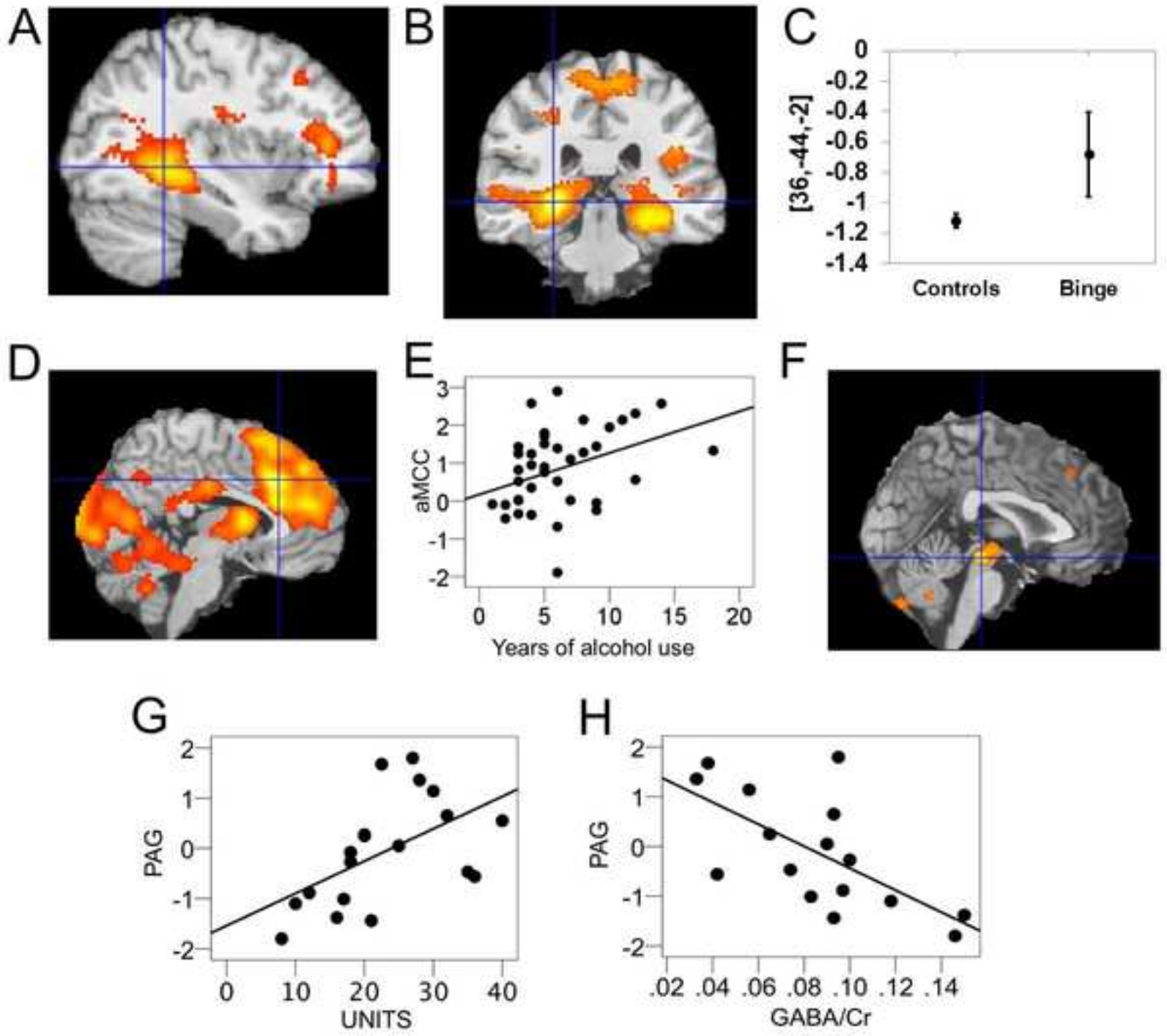
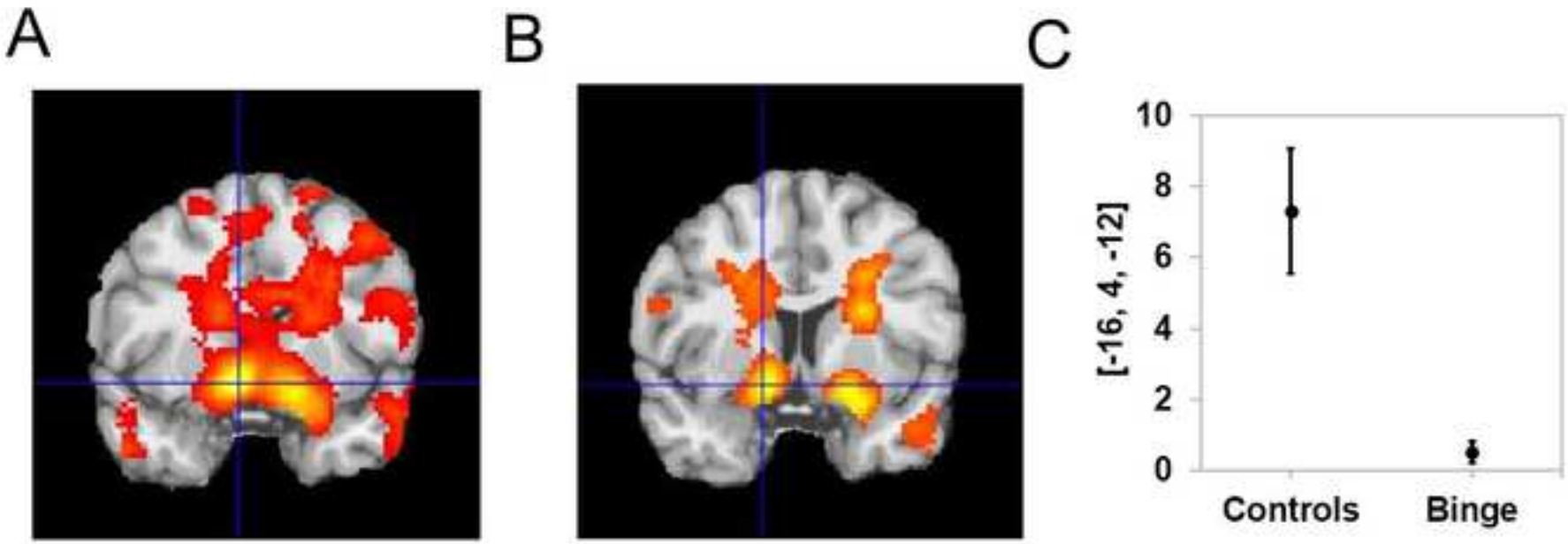


Figure 4



Alcohol Binge Drinking: Negative and Positive Valence System Abnormalities

Serenella Tolomeo, Jennifer A. McFarlane, Alex Baldacchino, George F. Koob, J. Douglas Steele

SUPPLEMENTAL INFORMATION

METHODS Definition of UK unit of alcohol and vouchers

RESULTS Participant characteristics, Analyses.

Table S1. Characteristics of participants.

Table S2. Within group activations and between group comparisons for Negative Valence System ('Loss events').

Table S3. Within group activations and between group comparisons for Positive Valence System ('Win events')

METHODS

One unit of alcohol in the UK is defined as 10 ml (8 grams) of pure alcohol and in the UK, containers of alcoholic drinks are normally labelled to indicate the number of alcohol units. Typical servings of alcohol contain 1 to 3 units of alcohol: e.g. a medium sized glass of red wine contains about 2 units of alcohol (https://en.wikipedia.org/wiki/Unit_of_alcohol).

During the fMRI paradigm, subjects agreed to accumulate as many 'win' events and possible and avoid as many 'loss' events as possible. They were told that they would receive a gift voucher for an amount related to their final win minus loss totals which could be exchanged in shops selling books or music. We decided this was preferable to money as we did not want to encourage subjects to buy alcohol.

RESULTS

Participant characteristics

The mean ± SD BDI and STAI-T scores of the BD participants was 4.9 ± 0.7 and 34.4 ± 8.8. The HC mean ± SD was 2.2 ± 4.4 and 30.7 ± 12.0, respectively. BD rated themselves as significantly more depressed and anxious than HC ($p=0.04$) and ($p=0.03$).

Analyses

Well matched behavior between groups is important to ensure comparable engagement with the task and so facilitate interpretation of neuroimaging results. There were no significant differences between binge drinkers and healthy control

groups for total number of rewards gained (p=0.18) or total number of losses inadvertently accumulated (p=0.7). *Post-hoc* pair wise comparisons with Bonferroni correction identified no significant difference in the number of wins between healthy controls and binge drinkers scanned on Monday versus Friday: number of rewards (p=0.12) and number of losses (p=0.9). These differences remained non-significant with age as a covariate. The average age of binge drinkers (25 years) was significantly less than for controls so correlations between age and the signals of interest were tested for. There were no significant correlations for brain regions of interest. This meant that age need not be used as a covariate in the second-level analyses. When this was done though, as expected it did not have a significant effect on the results. No significant differences between groups were found for GABA/Cr but a possible trend (p=0.06) was present (Table S1).

Table S1. Characteristics of participants.

	Controls (n=19)	Binge Drinkers (n=38)	p-values	Friday (n=19)	Monday (n=19)	p-values
Male/Tot	13/19	20/38	ns	10/19	8/19	ns
Age	33.7± 7.3	22.6±3.5	p<0.001	23±3.3	22.15±3.7	ns
SADQ	0.4±1.6	8.4±5.3	p<0.001	8.4±5.0	8.3±5.9	ns
Units	1.5±5.7	22.6±8.1	p<0.001	22.3±7.4	22.9±9.0,	ns
Smoking	17/19	34/38	ns	17/19	17/19	ns
AUDIT	0.5±1.7	13.4±4.2	p<0.001	13.2±3.6	13.7±4.9	ns
BDI	2.2±4.4	4.9±0.7	p=0.04	3.9±3.3	5.8±5.6	p=0.03
STAIS	26.6±8.1	28.4±7.9	ns	27.3±7.7	24.4±8.1	ns
STAIT	30.7±12.0	34.4±8.8	0.03	33.2±9.4	35.5±8.2	ns
SH	48.0±6.9	49.0±5.4	ns	50.8±4.4	47.2±5.9	ns
GABA/Cr	-	-	-	0.15±0.2	0.08±0.03	0.06
GLX/Cr	-	-	-	0.06±0.02	0.07±0.01	0.04
GABA/GLX	-	-	-	1.73±0.85	1.39±0.38	0.05

AUDIT=Alcohol Use Disorders Identification Test; BDI=Beck Depression Inventory-II; Cr= Creatine; Gamma-amino-butyric acid (GABA); glutamate-glutamine (GLX); SADQ=Severity of Alcohol Dependence Questionnaire; SH=Snaith-Hamilton; STAI-S = Spielberger state; STAI-T = Spielberger trait.

Table S2. Within group activations and between group comparisons for Negative Valence System ('Loss events').

	x	y	z	*t* value
Controls				
Activation				
Periaqueductal gray + dorsal raphe nucleus	-2	-32	10	5.7
Deactivation				
Left hippocampus	-36	-46	4	4.27
Right hippocampus	36	-44	-2	4.34
Left nucleus caudate	-24	0	-30	4.33
Right nucleus caudate	22	2	24	5.35
Left nucleus accumbens	-14	10	-10	3.47
Right nucleus accumbens	12	12	-12	3.8
Left medial orbitofrontal cortex	-20	28	-6	4.23
Right medial orbitofrontal cortex	18	32	-12	5.7
Binge Drinkers				
Activation				
Left anterior mid-cingulate cortex	-6	28	36	5.15
Left bilateral insula	-46	22	-8	5.49
Right bilateral insula	50	24	-8	5.49
Left nucleus caudate	-10	6	10	4.52
Right nucleus caudate	10	8	10	4.54
Deactivation				
Left amygdala	-20	-8	-26	2.98
Right amygdala	-16	-8	-26	3.32
Binge Drinkers > Controls				
Left hippocampus	-32	-40	-6	3.07
Right hippocampus	36	-30	-8	3.53
Left amygdala	-32	-2	-22	2.15
Right amygdala	28	-2	-30	2.79

Table S3. Within group activations and between group comparisons for Positive Valence System ('Win events').

	x	y	z	*t* value
Controls				
Left nucleus accumbens	-10	8	-6	8.05
Right nucleus accumbens	12	8	-14	7.13
Subgenual cingulate cortex	6	48	-10	6.39
Left amygdala	-28	-4	-18	3.83
Right amygdala	20	-6	-24	3.31
Left amygdala-hippocampal complex	-30	-12	-20	4.11
Right amygdala-hippocampal complex	22	-18	-18	4.53
Posterior cingulate cortex	4	-46	38	4.73
Binge Drinkers				
Subgenual anterior cingulate	-2	48	-20	4.58
Left hippocampus	-36	-16	-16	3.07
Right hippocampus	32	-18	-18	3.07
Controls > Binge Drinkers				
Left nucleus accumbens	-16	8	10	4.04
Right nucleus accumbens	14	6	-14	4.0
Left caudate nucleus	-18	12	26	2.52
Right caudate nucleus	24	10	18	3.67
Left amygdala	-24	0	-18	2.66
Right amygdala	16	0	-18	3.96

Allostasis theory describes in detail what happens when people develop alcohol or other drug problems which can ultimately result in addiction. However, the theory has been primarily developed from extensive pre-clinical work on animals. In this issue we show how fMRI can be used to non-invasively test allostasis theory predictions in binge alcohol drinking humans.